CHALLENGES IN CELLULAR, TISSUE, AND GENE THERAPY PRODUCT DEVELOPMENT IN THE CT ARENA

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- Regulatory/review responsibility for tissues, cellular, gene therapies, and xenotransplantation products
- Regulatory programs and scientific research to assure the continued safety, identity, purity, and potency of these products
- Collaborative reviews for combination products that consist of cells/tissues combined with a drug or device

OCTGT Counterterrorism Strategy

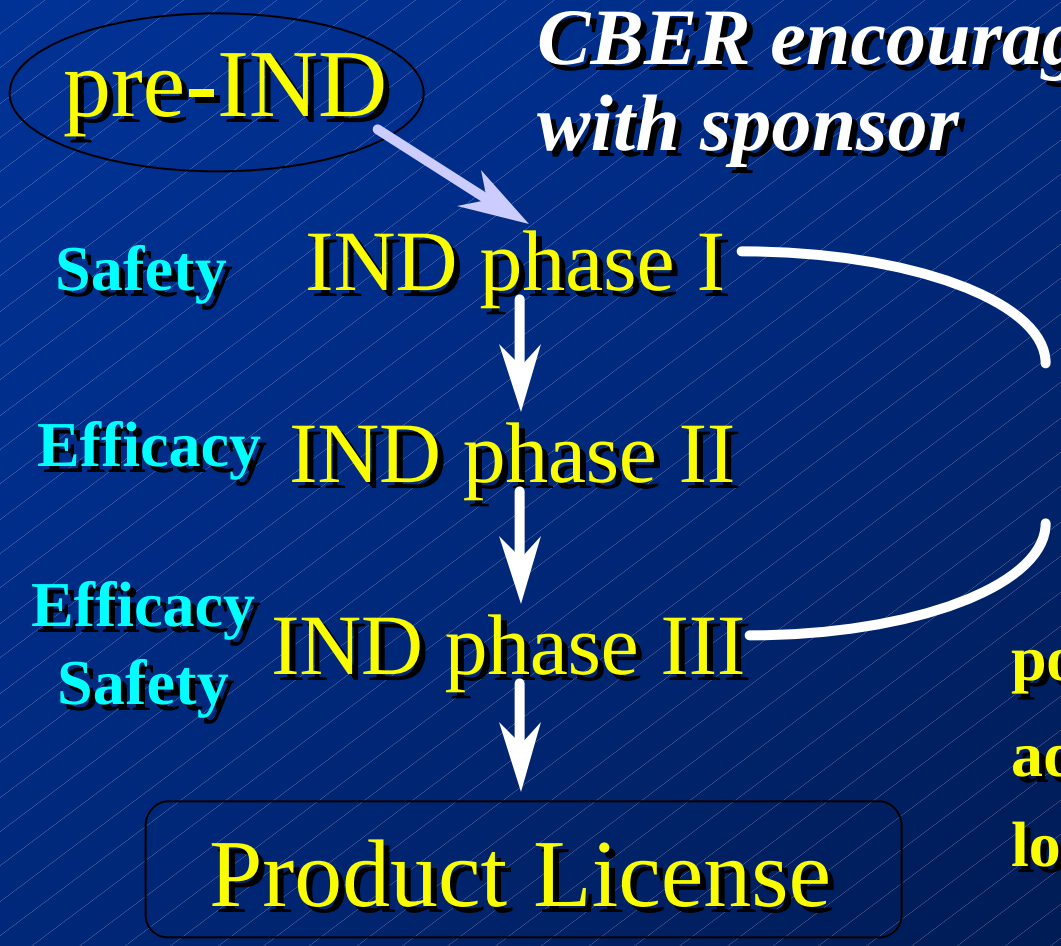
- Encourage and facilitate development of novel cellular, tissue, and gene therapy products as medical countermeasures
- Safeguard integrity of tissue supply

Regulatory Concerns Common to all Biologicals

- Safety, efficacy, identity, purity, potency
- Regulation of both product and process
- Quality control of product and intermediates
- Reproducibility of lots

Challenges of Expedited CT Development

Regulatory and Approval Process



CT Product Development

pre-pre-IND

pre-IND

CBER encourages VERY early and FREQUENT interaction with sponsor

Safety IND phase I

Efficacy IND phase II

Efficacy Safety IND phase III

Product License Phase IV

Product — Animal Rule

PharmTox

Clinical — Human Experience

OCTGT Counterterrorism Strategy

- **Biological, radiological, chemical, traumatic injuries**
- **Could be addressed with cell, tissue, gene therapy-based products**

Repair, Replace, Restore, Regenerate

Challenges for Tissues

- **Safeguard integrity of tissue supply**
  - Devise appropriate donor deferral contingencies
    - Infectious agent, radiological, chemical exposure
  - Adapt new donor screening tests
  - Assure that affected individuals do not cause inadvertent spread/exposure

Tissues: cGTPs

- CGTP requirements govern the methods used in, and the facilities used for, the manufacture of HCT/Ps
- Intended to prevent the introduction, transmission and spread of communicable disease, and to preserve function and integrity

Extra vigilance when urgent need for tissues exists

FDA Measures to Facilitate Potential Use of Human Tissue for CT/BT

- Communication with industry
  - regional shortages; emergency plans
- Temporary exceptions to certain FDA requirements, when benefit outweighs risk
  - E.g., waiver of requirement to use infectious disease test kits validated for cadaveric blood samples
- Stockpiling of tissues
  - However, many tissues have short shelf life—e.g., corneas, “fresh”refrigerated skin

Repair, Replace, Restore, Regenerate

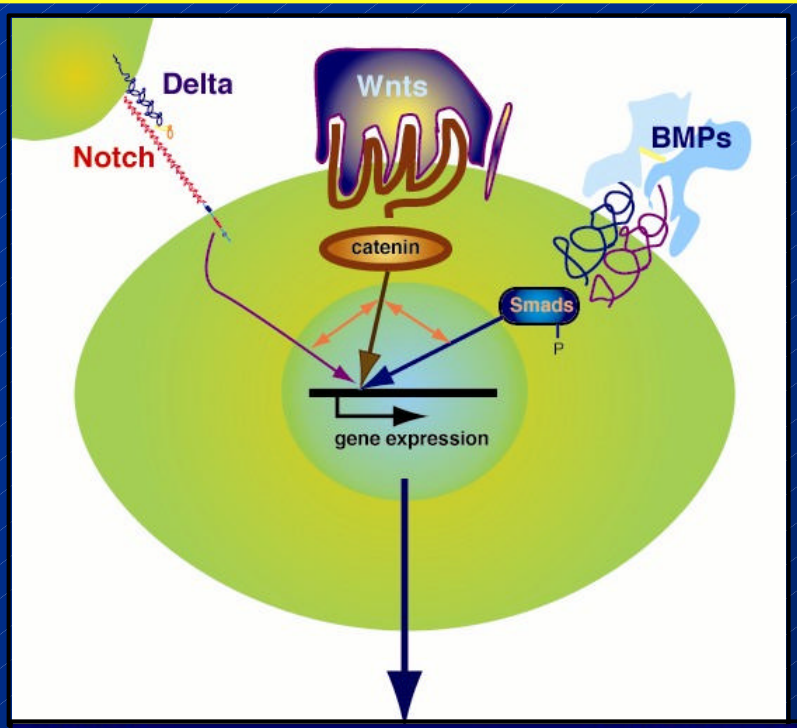
- **Cellular Therapies**
- **Gene Therapies**
- **Cellular Therapies + Gene Therapies**
- **Tissue Engineering**
  - Combination Cell/Tissue with Device/Gene Therapy/Recombinant Protein

Combination Products: Multiple FDA Centers

CBER Research and Regulation

- **CBER Research/Review Model**
  - Scientists / Clinicians: lab based and full-time review staff
- **Challenges for CT use of cellular, tissue, and gene therapies**

CBER research relevant to stem cells: Control pathways in development



Cell fate	Cell Therapies
Cell renewal ('Stem-ness')	Stem Cells
Reprogramming (nuclear transfer)	"Cloning"
Fertilization/implantation	ART
Tissue organization	Combination Products
Organogenesis	Tissues, Regeneration and Repair

Signaling pathways crucial in differentiation and development:

Conserved in all metazoans
(Work in model organisms cheaper, faster)

Affect many stages of development
Cell types, cell fates
Repair and regeneration

Importance of the microenvironment

Cell Therapy Challenges

- **Cell therapies hold great promise but present challenges to CBER**
  - **Measures of safety, quality, potency, efficacy complex**
    - sufficient characterization
    - appropriate differentiation
    - transformation
    - affected by *in vitro, in vivo* conditions

Cellular Product Testing

- Donor
- Incoming cellular or tissue sample
- Components and reagents used in manufacturing
  - Animal product- FBS, BSA, enzymes
  - Cell culture- MAbs
- Manufacturing intermediates
- Final product

Cellular Product Safety

- Sterility (21 CFR 610.12)
- Mycoplasma (21 CFR 610.30)
- Freedom from Adventitious Agents
- Pyrogenicity/Endotoxin (21 CFR 610.13)

Cellular Product Identity/Purity

- Cell Viability
  - Recommend >70%
  - Freedom from Extraneous Material
  - Media Components
    - E.g.: serum, cytokines
- Phenotypic Analysis
  - Cell Types
  - Quantitative assessment of each cell type present

Reproducibility

Cellular Product Biological Activity

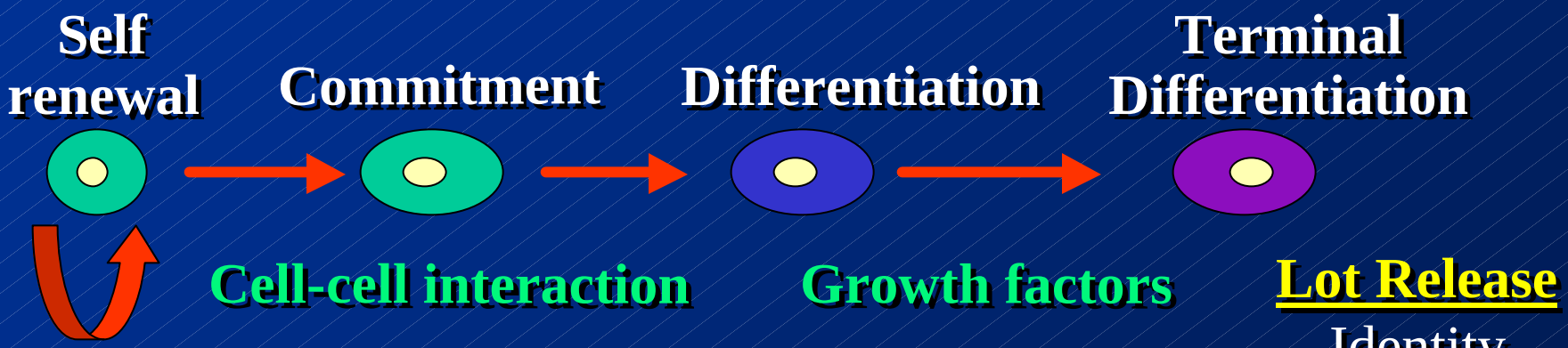
- Assay that correlates with function of product
  - Gene expression pattern
    - *In vitro* differentiation correlated with specific gene expression
  - Expression of antigen
    - Cytokine release assay correlated with expression of protein

Correlation often challenging

Characterization

Gene expression profile,
Antibodies, Enzymes,
In vitro differentiation

Developmental Stages
Exogenous Influences
Manufacturing Concerns



Lot Release

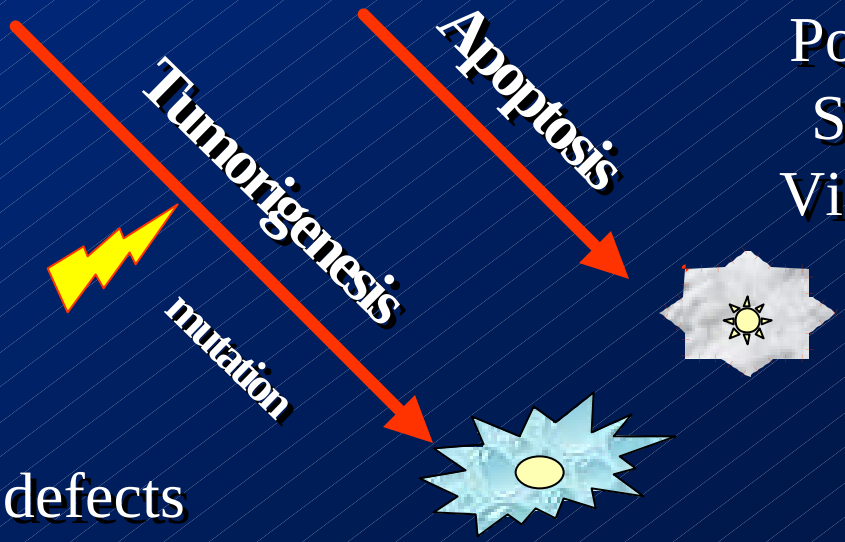
Identity
Potency
Safety
Viability

Manufacturing

Cell Banks
Feeder Layers
Growth Factors
Cell Characterization

Screening

Donors, Viruses, Genetic defects



Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs) - 8/15/2003

http://www.fda.gov/cber/guidelines.htm

Gene Therapy Product Manufacturing

- Vector manufacturing
  - Vector construction, characterization
  - Cell Banks
  - Virus Seed Stocks
  - Plasmid stocks
  - Vector Production/Purification Methods
  - Formulation of Final Product
  - Storage/Stability

Gene Therapy Product Safety

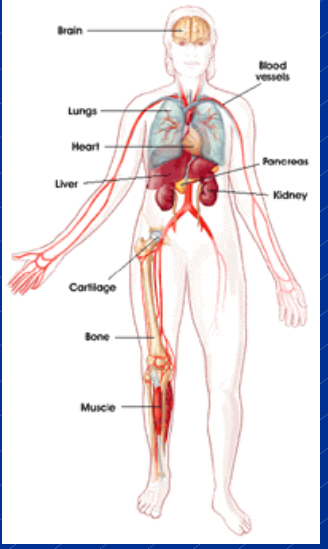
- **Safety Testing**
  - **Sterility**
  - **Mycoplasma**
  - **Adventitious Virus**
    - **in vitro and in vivo virus**
    - **bovine and porcine viruses (or certified reagents)**
    - **human viruses: EBV, HBV, HCV, CMV, HIV 1&2, HTLV 1 & 2, B19, AAV, (others)**
  - **Replication Competent Virus**

Gene Therapy Product Characterization

- Identity
  - restriction map+southern blot
  - nucleic acid sequence
- Activity
  - transgene specific
- Titer
- Purity
  - cell substrate DNA, RNA, protein, other reagents
- Stability
- Potency
  - Qualified assay required by end of phase II
  - Assay should reflect intended biological effect of product

Gene Therapy: Unique Safety Concerns

- Viral Vectors: rescue of replicating virus
- Contamination of product with viruses from cells used in manufacture
- Inadvertent germ-line gene transfer
- Integration into genome
  - Insertional mutagenesis



CT Product Development

- CBER-Sponsor interactions: early and often
- Encourage novel cell, tissue, and gene therapy products
- Repair, replace, restore, regenerate

CBER/OCTGT Contact Information

- **PHONE: 800-835-4709 or 301-827-2000**
- **INTERNET: http://www.fda.gov/cber**
- **Send e-mail to: OCTMA@CBER.FDA.GOV or MATT@CBER.FDA.GOV**

- **CBER Regulatory and Guidance Documents on the Internet at: http://www.fda.gov/cber/guidelines.htm**

- **Bauer@CBER.FDA.GOV**
- **301-827-0684**

Information OCTGT Products

- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy, March 1998.
- PTC in the Characterization of Cell Lines to Produce Biologicals, CBER, FDA, 1993.
- Proposed Approach to Regulation of Cellular and Tissue-Based Products, February 1997.
- ICH Harmonized Tripartite Guideline: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Information on HCT/Ps

- Website at www.fda.gov/cber/tiss.htm
  - Form 3356 – Registration/Listing
  - Published documents and letters
  - Meeting minutes/summaries/transcripts/presentations
- E-mail address for registration questions tissueregs@cber.fda.gov
- HCTERS Queries – information on registered establishments http://intranet.fda.gov/cber/tissue/hcters.htm